REMARKS

Reconsideration of the present application is respectfully requested.

Claims 76-77, 92-93, 95, 97-99, 106-107 and 109-111 are cancelled with this amendment. Claims 112-120 have been added.

Claims 76-79, 90-93, 95-99, 103, 105-108, 110 and 111 are rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner indicates that the recitation of "plant seed protein" is indefinite as it is unclear whether it means any protein that is or can be produced in a plant seed, or proteins that are only produced in plant seeds.

The claims have been rewritten to recite, "a polynucleotide encoding a native plant seed protein or a native plant seed protein modified to contain about 7 mole % to about 40 mole % lysine and/or about 6 mole % to about 40 mole % of a sulfur containing amino acid". Support for native plant seed proteins is found on page 8, line 3 to page 9, line 9; page 12, line 15 to page 13, line 9. Support for modified plant seed proteins is found on pages 9-12, the Examples and the sequences. Support for the mole % ranges is found on page 6, line 21 to page 7, line 4.

Claim 78 has been amended to remove "plant derived".

Claims 90-91 have been amended to depend from claim 112. Claims 92-93 are cancelled.

Claims 76-79, 90-93, 95-99, 103 and 105-111 remain rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The rejection is maintained for the reasons of record set forth in the Official action mailed December 11, 2001.

In the Official action mailed December 11, 2001 the Examiner repeats the rejection for the reasons set forth in the Official action mailed 5/18/99, the Official action mailed 11/22/99 the Official action mailed 4/21/00, the Official action mailed 8/9/00 and the Official action mailed 6/25/01.

In the Official action mailed December 11, 2001 the Examiner states that Applicant does not describe other modified nucleic acids.

The rejection is believed improper for the following reasons. As discussed in detail in previous responses and again below, numerous wild type and modified polynucleotides are disclosed in the application and are also known in the art. Copies of many references were supplied to the Examiner in the amendment and IDS filed September 25, 2001.

The Examiner states that it is improper to incorporate essential material by reference and that the Applicant has not satisfied the written description requirement.

It is impractical to submit all possible sequences that could be used in the claims. Based on the state of the art and the disclosure provided in the present application, one skilled in the art would readily be able to make and use the present application. In *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQD 1111, 1117 (Fed. Cir. 1991) the court held that to satisfy the written description requirement, "the applicant must convey with reasonable clarity to those skilled in the art that ... he or she was in possession of the invention."

With regard to written description, 35 U.S.C. § 112, P 1 ("The specification shall contain a written description . . . in . . . concise, and exact terms . . . .") (emphasis added). In furtherance of this policy goal, the Federal Circuit has admonished against including in the specification material that is known in the art. See, e.g., *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1534, 3 U.S.P.Q.2D 1737, 1743 (Fed. Cir. 1987) ("A patent need not teach, and preferably omits, what is well known in the art."); *Howarth*, 654 F.2d at 105, 210 U.S.P.Q. at 691 ("An inventor need not, however, explain every detail since he is speaking to

those skilled in the art."); *In re Gay*, 50 C.C.P.A. 725, 309 F.2d 769, 774, 135 U.S.P.Q. 311, 316 (CCPA 1962) ("Not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be."). Use of incorporation by reference makes the written description more concise. Requiring inventors to include every imaginable detail of a structure corresponding to a claimed means, including those widely understood by persons of ordinary skill in the art, would be the antithesis of conciseness and would result in exceedingly lengthy patents. In any event, by codifying the requirement of conciseness in section 112, P 1, Congress has expressed its preference."

Clearly the applicant provided adequate disclosure for one skilled in the art to realize that the Applicant was in possession of the invention. It is submitted that the Examiner has not fully appreciated the "level of skill in the art". Such examination is required for the evaluation of written description to determine whether the inventors had possession of the invention. The applicant has provided extensive literature and patent citations to describe suitable materials useful in practicing the present claimed invention. The citations and copies of publications were provided previously.

The Examiner states that the Applicant does not state which pending application comprises a description of a modified ESA nucleic acid and that the instant application does not claim priority to that application. The present application is amended to cite the US patent for ESA.

Further, the ESA nucleic acid sequence is found in SEQ ID NO: 6, (2199-2675) (see Table 2, page 40, of the present application). The hordothionin (HT) SEQ ID NO: 1, (3361-2947), high lysine hordothionin (HT12) SEQ ID NO: 2 (3361-2947) and the high lysine chymotrypsin inhibitor gene (also called barley high lysine gene or BHL) SEQ ID NO. 7 (2199-2450) are found in the sequences filed and identified in Table 2 of the present application. Additional HT12 sequence modifications are found in SEQ ID NOS: 10-13.

As discussed in the amendment filed by the Applicant on March 11, 2002, numerous suitable genes were known in the art, many identified in the application. The information is provided again for the Examiner's convenience. The present application was amended to include sequence information from publications cited in the present application.

The Examiner is familiar with the Rao patents as they were cited in 1449 forms. US Ser. No. 08/838,763 cited on page 9, line 6 of the present application is now US Pat. No. 5,990,389, cited on a 1449 form as A18. US Ser. No. 08/824,379 cited on page 9, line 7 of the present application is now US Pat. No. 5,885,801 cited on a 1449 form as A20. US Ser. No. 08/824,382 cited on page 9, line 7 of the present application is now US Pat. No. 5,885,802, cited on a 1449 form as E2. The 10 kD zein storage protein from maize is disclosed in Kirihara et al. 1988, Mol. Gen. Genet. 211: 477-484, a copy of which was previously provided. Sulfur-rich 10 kD rice prolamin is disclosed in Masumura et al., Plant Mol. Biol. 12:123-130, 1989, (A25 on the 1449 form and cited on page 13, lines 7-8 of the present application, SEQ ID NOS: 20-21). The maize gene encoding methionine-rich 15 kD zein protein is found in Pedersen et al., J. Biol. Chem., 261, 6279-6284 (1986), (A26 on the 1449 form and cited on page 13, lines 5-6 of the present application, SEQ ID NOS: 16-17). The gene encoding the Brazil nut protein is found in Altenbach et al., Plant Mol. Biol., 8: 239 (1987), a copy of which was previously included. The gene encoding a high methionine maize 10 kD zein is found in Kirihara et al., Gene, 7, 359-370 (1988), (A22 on the 1449 form submitted and cited on page 13, lines 6-7 of the present application). Pea genes encoding high sulfur protein are disclosed in Higgins et al., J. Biol. Chem., Vol. 261, No. 24, pp. 11124-111310 (1986), (A21 on the 1449 form and cited on page 12, lines 18-19 of the present application, SEQ ID NOS: 14-15). A gene encoding a methionine rich sunflower protein is found in Lilley, et al., Proceedings of the World Congress on Vegetable Protein Utilization in Human Foods and Animal Feedstuffs; Applewhite, T.H. (ed.), American Oil

Chemists Soc., Champaign, IL, pp. 497-502 (1989), (A23 on the 1449 form and cited on page 13, lines 1-5 of the present application).

Other suitable genes include 12S seed storage protein gene from rapeseed disclosed in Ryan et al., Nucleic Acids Res., 17 (9): 3584 (1989) a copy of which was previously provided. The sunflower 2S albumin gene is disclosed in Allen et al., Mol. Gen. Genet., 201 (2): 211-218, (1987) a copy of which was previously provided. The maize albumin b-32 gene is disclosed in Di Fonzo et al., Mol. Gen. Genet., 212 (3): 481-487 (1988), a copy of which was previously provided. The napin gene is disclosed in Joseffson et al., J. Biol. Chem., 262 (25): 12196-12201 (1987) and Scofield and Couch, J. Biol. Chem., 262 (25): 12202-12208 (1987) copies were previously provided. The B1 hordein gene is disclosed in Forde et al. Nucleic Acids Res. 13 (20): 7327-7339 (1985), a copy of which was previously provided. The wheat alpha and beta gliadin genes were described in Sumner-Smith et al., Nucleic Acids Res., 13 (11): 3905-3916 (1985), a copy of which was previously provided. Wheat gliadin is also disclosed in Anderson et al., Nucleic Acids Res., 12(21): 8129-8144 (1984), a copy of which was previously provided. The pea legumin gene is disclosed in Lycett et al., Nucleic Acids Res., 12 (11): 4493-4506, a copy of which was previously provided. Various maize zeins are disclosed in Heidecker and Messing, Nucleic Acids Res., 11 (14): 4891-906 (1983), copies were previously provided. The alpha, alpha', and beta-subunits of soybean 7S seed storage protein is disclosed in Schuler et al., Nucleic Acids Res., 10 (24): 8245-8261 (1982) and Schuler et al., Nucleic Acids Res., 10 (24) 8225-8244 (1982) copies are enclosed. The sunflower 11S gene is described in Vonder Haar et al., Gene, 74 (2): 433-443 (1988), a copy of which was previously provided. The pea convicilin gene is disclosed in Bown et al., Biochem. J., 251 (3): 717-726 (1988), a copy of which was previously provided.

Claims 76-79, 90-93, 95-99, 103 and 105-111 remain rejected under 35 USC 112, first paragraph because the specification is enabling only for claims limited to

transformed cereal plant seed having an elevated lysine, methionine and cysteine content (about 10% to about 35% by weight compared to untransformed cereal plant seed) comprising the modified hordothionin gene, vectors, plant cells and transformed plants comprising the gene. The Examiner states that the specification does not enable any person skilled in the art to which it pertains to make and or use the invention commensurate in scope with the claims.

The Examiner indicates that the rejection is maintained for reasons set forth in the Official action mailed December 11, 2001.

The Official action mailed December 11, 2001 repeats the rejection for the reasons of record set forth in the Official action mailed 6/25/01 as applied to Claims 75-94.

The Official action mailed 6/25/01 repeats the rejection for the reasons of record set forth in the Official action mailed 5/18/99 as applied to claims 1-21, the Official action mailed 11/22/99 as applied to claims 6, 7, 14-17, and 21-35, the Official action mailed 4/21/00 as applied to claims 36-56 and the Official action mailed 8/9/00 as applied to claims 57-74.

As discussed in detail above and in previous responses, the specification provides the necessary disclosure for one of skill in the art to make and use the invention commensurate in scope with the present claims. Table 1, page 40 of the specification, demonstrates increased lysine obtained by using a construct comprising HT12 and an endosperm-preferred promoter. A 1.132 Declaration signed by co-inventor Rudolf Jung and submitted October 18, 1999 provides results that demonstrate the effectiveness of using a construct comprising ESA and an endosperm-preferred promoter to increase lysine, cysteine and methionine.

It is submitted that the present specification and the prior art provide extensive information on polynucleotides suitable for increasing the level of lysine and/or a sulfur-containing amino acid. The Examiner has not provided any evidence that the information disclosed in the application does not lead to the beneficial results of the present claims.

In the 11/22/99 Official action the Examiner responded that no specific guidance with respect to ESA is provided in the specification.

Applicant submits that the sequence for the ESA polynucleotide is found in the original specification as SEQ ID NO:6. Information regarding the ESA protein is found in US Pat. No. 5,850,016 which is incorporated by reference in the present application. The present application has been amended to replace the US Ser. No. with the US Pat. No.

Further in the 11/22/99 Official action the Examiner states that proper protein expression and folding would be required, and phenotypes such as lethality, sterility, or other deleterious effects would necessarily need to be avoided.

The issues of lethality, sterility or other deleterious affects are reduced by the present claimed invention. Using typical seed proteins or modified seed proteins reduces the deleterious affects and increases the success of protein expression. Using an endosperm-preferred promoter to express seed proteins further increases the chance of success for protein expression and reduces the affect of issues of lethality, sterility or other deleterious affects. However, a range of protein expression and phenotypic affects are typical in producing transgenic events. A selection process is usually required to select the most desirable events. Such selection is routine. Again the present claimed invention is designed to minimize problems of expression, lethality, sterility or other deleterious affects.

The Examiner states that Applicant has provided no specific guidance with respect to what amino acids could be substituted without affecting expression and folding of the protein, and without resulting in detrimental phenotypes.

Applicant has provided specific examples of native and modified proteins (derivatives or variants) from the present application and from published literature. Examples of modified proteins include HT12, ESA and BHL.

The present specification also provides general guidelines for preparing other derivatives and variants. High lysine and high sulfur containing proteins are described on page 6, line 21 to page 7, line 4 of the present application. Once a

sequence has been determined, appropriate polynucleotides can be prepared by site-directed mutagenesis as discussed on page 8, lines 8-16 of the present application. This information in conjunction with "the knowledge of one skilled" in the art provides sufficient guidance to produce derivatives and variants.

As stated in *In re Wright*, 99, F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); MPEP § 2164.04, the enablement requirement is satisfied if the specification describes any method for making and using the claimed invention that bears a "reasonable correlation" to the entire scope of the claims. Applicants submit that many methods that correlate to the present claims have been described in the present application.

Polynucleotide sequences encoding proteins with high lysine and/or a high sulfur protein can easily be tested for expression using known methods. "That one skilled in the art must perform some preliminary tests or experiments before he can make or use the invention does not invalidate the patent" on the basis of section 112. *Atlas Powder Co. v. E. I. Du Pont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984). Thus, polynucleotides encoding for the desired amino acid expression can easily be found without undue experimentation.

In re Wands, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988) lists eight considerations for determining whether or not undue experimentation would be necessary to practice an invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

When determining the quantity of experimentation necessary, the focus is not on the amount of experimentation necessary to practice the entire genus, but the amount of experimentation required to practice any particular member. This concept is the central holding of *In re Wands* where the claims read on the use of any IgM antibody that possessed a particular binding affinity.

The Examiner maintains that the undue experimentation lies in the process of identifying, prior to functional characterization, which sequences so generated are likely to encode a functional protein.

However, the *Wands* court recognized that it would require an infinite amount of experimentation to obtain every single possible IgM antibody that could be generated with the specified affinity. Accordingly, the court focused on the amount of experimentation necessary to practice any particular IgM antibody with the recited binding affinity and not the amount of experimentation required to practice the entire genus.

With regard to the remaining Wands factors, Applicant has discussed extensively the amount of direction or guidance presented in the application and the level of skill in the art. Numerous references have been provided as well as the information in the application. The Applicant has provided working examples in the application and in a 1.132 Declaration. Thus meeting the *Wands* factor relating to the presence or absence of working examples of the invention. With regard to the nature of the invention, the Applicant submits that the claim scope is commensurate with the enablement provided. The state of the prior art provides background for the components useful for the invention. The Applicant provides the claimed combination. As discussed above and in previous responses Applicant has provided many references indicating the relative skill of those in the art is high. The scope of the claims is appropriate based on the predictability or unpredictability of the art.

Claims 76-79, 90-93, 95-99, 103 and 105-111 remain rejected under 35 USC 102(e) as being obvious over Falco et al (US Pat. No. 5,773,691). The Examiner states that the rejection is maintained for the reasons of record as set for claims 76-79, 90-93 and 95-111 in the Official action mailed December 11, 2001. The latter rejection was repeated for the reasons set forth in the Official action mailed 6/25/01.

It is not clear whether the rejection is an anticipation or an obviousness rejection based on 102(e). Clarification of the rejection is requested.

The Examiner issued a 102(e) anticipation rejection in the Official action mailed December 11, 2001. The rejection is based on the claim term "plant derived polynucleotide". The Examiner indicates that "plant derived polynucleotide" reads on essentially any polynucleotide, because any polynucleotide can be derived from a plant.

The rejection is considered moot as applied to the current claims. The current claims require a polynucleotide encoding a native seed protein or a modified native seed protein.

It is submitted that Falco does not disclose or suggest the combination recited in the present claims, "a seed endosperm-preferred promoter operably linked to a polynucleotide encoding a native plant seed protein or a native plant seed protein modified to contain about 7 mole % to about 40 mole % lysine and/or about 6 mole % to about 40 mole % of a sulfur-containing amino acid".

Claims 76-79, 90-93, 95-99, 103 and 105-111 remain rejected under 35 USC 102(a) as being obvious over Rao et al. (US Pat. No. 5,885,802) in view of the Applicants admission. The rejection is maintained for the reasons of record as set forth for claims 76-79, 90-93 and 95-111 in the Official action mailed December 11, 2001. In the Official action mailed December 11, 2001 the rejection is repeated for the reasons of record as set forth in the Official action mailed 6/25/01.

In the Official action mailed 6/25/01 the Examiner states the following:

> It would have been *prima facie* obvious to one of ordinary skill in the art at the time of Applicant's invention to modify the invention of Rao to substitute an endosperm-specific promoter, as admitted by Applicant to have been known in the art, for the constitutive promoter, because the invention was clearly directed to modification of seed tissue, and especially endosperm. The different promoters are functional equivalents, and it would have been obvious to substitute one functional equivalent for

> another. Hordothionine is a seed protein and hence expression in the seed (the major portion of which is endosperm) would be expected to be successful. Also, it was well known in the art that increased nutritional value of seeds was particularly desirable given the importance of grains as a food source in the impoverished regions of the world. One would have had a reasonable expectation of success in view of the success of Rao.

The Examiner is requested to support the above conclusory statements, for example that promoters are functional equivalents.

Rao discloses a high methionine engineered hordothionin protein.

In column 5, lines 7-9 the '802 patent reads that "the plant expression cassette preferably includes a strong **constitutive** promoter sequence at one end to cause the gene to be transcribed at a high frequency", thus teaching away from using an endosperm-preferred promoter. The current claims require an endosperm-preferred promoter.

Therefore, there is no motivation to use an endosperm-preferred promoter to produce the protein of Rao '802. "Even when obviousness is based on a single prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference", *In re Kotzab*, 208 F.3d 1352, 54 USPQ2d 1308 (Fed. Cir. 2000).

The Examiner has provided no motivation to make the necessary modifications and thus has not made a *prima facie* obvious case over Rao '802.

Claims 76-79, 90-93, 95-99, 103 and 105-111 remain rejected under 35 USC 102(a) as being obvious over Rao et al. (US Pat. No. 5,990,389) in view of Applicant's admission. In the Official action mailed December 11, 2001 the rejection is repeated for the reasons of record as set forth in the Official action mailed 6/25/01.

In the Official action mailed 6/25/01 the Examiner states the following:

> It would have been prima facie obvious to one of ordinary skill in the art at the time of Applicant's invention to modify the invention of Rao to substitute an endosperm-specific promoter, as admitted by Applicant to have been known in the art, for the constitutive promoter, because the invention was clearly directed to modification of seed tissue, and especially endosperm. The different promoters are functional equivalents, and it would have been obvious to substitute one functional equivalent for another. Hordothionin is a seed protein and hence expression in the seed (the major portion of which is endosperm) would be expected to be successful. Also, it was well known in the art that increased nutritional value of seeds was particularly desirable given the importance of grains as a food source in the impoverished regions of the world. One would have had a reasonable expectation of success in view of the success of Rao.

The Examiner is requested to support the above conclusory statements, for example that promoters are functional equivalents.

Rao discloses a high lysine engineered hordothionin protein. The '389 patent also discloses that "the plant expression cassette preferably includes a strong **constitutive** promoter sequence at one end to cause the gene to be transcribed at a high frequency". See column 4, lines 65-67 of the '389 patent. Thus the '389 patent also teaches away from using an endosperm-preferred promoter. The current claims require endosperm-preferred promoter.

The Examiner has provided no motivation to make the necessary modifications and thus has not made a *prima facie* obvious case over Rao '389.

"When determining the patentability of a claimed invention which combines two known elements, the question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the

combination." *In re Beattie*, 974 F.2d 1309, 1311-12, 24 U.S.P.Q.2D 1040, 1042 (Fed. Cir. 1992) (quoting *Lindemann*, 730 F.2d at 1462, 221 U.S.P.Q. at 488).

In the present case, the prior art as a whole would lead one away from using the present claimed combination. Nothing in the prior art as a whole would suggest the desirability or the likelihood of success when combining the elements of the present claimed invention, i.e. a seed endosperm-preferred promoter operably linked to a polynucleotide encoding native seed protein or a modified native seed protein.

In the Official Office action mailed 3/11/03 the Examiner questions the value of the results in the specification and the Declaration. It is submitted that absent a *prima facie* showing of obviousness, no unexpected results are necessary.

However, it is noted that the results in Table 1 in the present application demonstrate increased lysine in the transgenic seed comprising a seed-endosperm preferred promoter and polynucleotide encoding a modified native seed protein. The HT12 protein in Table 1 is high in lysine, not cysteine or methionine. The ESA protein is high in cysteine and methionine which is consistent with the results in the prior 1.132 Declaration filed 10/18/99.

Claims 76-79, 90-93, 95-99, 103 and 105-111 remain rejected under 35 USC 103(a) as being anticipated by Jaynes et al. (US Pat. No. 5,811,654) in view of the Applicants' admission. It is presumed the Examiner meant to say "obvious over" as is consistent with 35 USC 103(a) and with the prior rejections.

The rejection is maintained for the reasons of record as set forth for claims 76-79, 90-93 and 95-111 in the Official action mailed December 11, 2001. The Official action mailed December 11, 2001 repeated the rejection for the reasons of record as set forth in the Official action mailed 8/9/00 as applied to Claims 57-74, the Official action mailed 4/21/00 as applied to Claims 36-56, and the Official action mailed 6/25/01. It is noted that the later identified claims are no longer in the application.

The Examiner states the following:

> The motivation provided by Examiner lies in the Jaynes reference itself. As Jaynes shows increases in amino acid composition in the seed (the major portion of which is the endosperm), one would have been motivated to substitute a seed-specific, or endosperm-specific promoter to further increase or to limit increases to the seed/endosperm tissue. The teachings of Jaynes are clearly directed to increasing amino acid composition in seeds. Hence, it would have been an obvious modification to substitute and endosperm-specific promoter.

Jaynes does not disclose or suggest a using an endosperm-preferred promoter. Jaynes does not disclose or suggest using a native seed protein or a modified native seed protein. Jaynes does not disclose or suggest using the combination of the two. It is submitted that the Examiner is relying on the disclosure of the present application to justify the rejection.

The Examiner has provided no motivation to use an endosperm-preferred promoter to increase lysine or a sulfur-containing amino acid content. The fact that endosperm-preferred promoters are known in the art does not provide the necessary motivation. "Even when obviousness is based on a single prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference", *In re Kotzab*, 208 F.3d 1352, 54 USPQ2d 1308 (Fed. Cir. 2000).

Thus, the Examiner has not made a *prima facie* obvious case over Jaynes '654.

In view of the above comments and amendments, withdrawal of the outstanding rejections and allowance of the remaining claims is respectfully requested. In the event that the Examiner maintains rejections, the Applicant requests that the rejections be addressed to the current claims.

Respectfully submitted,

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